

N-Hydroxyphthalimide-catalyzed radical addition of 1,3-dioxolanes and molecular oxygen to alkenes under ambient conditions: a new route to β -oxycarbonyl compounds

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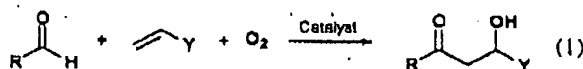
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A novel catalytic hydroxyacylation of alkenes using 1,3-dioxolanes and molecular oxygen has been developed, and the reaction of 2-methyl-1,3-dioxolane with methyl acrylate under dioxxygen atmosphere in the presence of catalytic amounts of NHPI and $\text{Co}(\text{OAc})_2$ produced the corresponding adduct in 81% yield.

Addition of aldehydes to terminal alkenes has received attention as a method for the synthesis of ketones from aldehydes.¹ The frequently used methodologies are the direct hydroacylation of alkenes with aldehydes by transition-metal catalysts¹ and the addition of acyl radicals to alkenes bearing electron-withdrawing substituents such as fumarate by radical initiators.² If the concomitant introduction of acyl and hydroxy moieties to alkenes can be carried out by a cascade reaction, this type of reaction is referred to as *hydroxyacylation* and would provide a novel route to β -oxycarbonyl compounds which constitute important structural subunits in key intermediates leading to pharmaceuticals [eqn. (1)].³ Although there is one report on the hydroxyacylation of alkenes like acrylates with acyl radicals from aldehydes using dioxxygen as a hydroxy source assisted by a cobalt(II) Schiff-base complex,⁴ the attempt was not fully successful due to the decarbonylation from acyl radicals as well as the reaction of acyl radicals with O_2 leading to carboxylic acids which cause undesired side reactions.

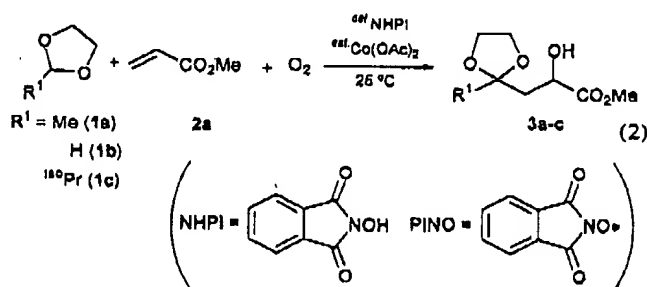
Hydroxyacylation



To overcome these drawbacks arising from acyl radicals, we employed 1,3-dioxolanes, masked aldehydes, as an acyl source in place of an aldehyde.⁵ This paper describes the development of a novel catalytic method leading to β -hydroxy carbonyl compounds after deprotection under acidic conditions.

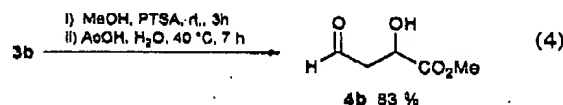
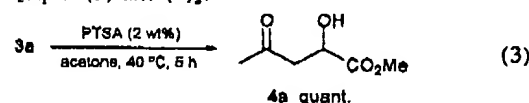
Recently, we have shown that *N*-hydroxyphthalimide (NHPI) combined with a $\text{Co}(\text{II})$ species serves as a catalyst for the generation of alkyl radicals from alkanes even under ambient conditions, and that the resulting alkyl radicals are readily captured by O_2 to give oxygenated products.⁶ In this catalytic system, phthalimide *N*-oxyl (PINO) is the active species abstracting hydrogen atoms from the alkanes.^{6a} This finding prompted us to study the generation of α,α -dioxalkyl radicals from 1,3-dioxolanes and their addition to alkenes using the NHPI/ $\text{Co}(\text{II})$ - O_2 catalytic system [eqn. (2)].

At the beginning, a mixture of 2-methyl-1,3-dioxolane (1a) (15 mmol) and methyl acrylate (2a) (3 mmol) was allowed to react under O_2 (1 atm) in the presence of NHPI (5 mol%) and a small amount of $\text{Co}(\text{OAc})_2$ (0.05 mol%) at rt for 3 h (Table 1, Run 1).[†] The apparent hydroxyacylation based on the concomitant introduction of a dioxalkyl radical and a hydroxy group to 2a was achieved to form β -hydroxy ketal (3a) in 81% yield. In a previous paper, we showed that a $\text{Co}(\text{III})$ -dioxxygen complex derived from the $\text{Co}(\text{II})$ species and O_2 assists the formation of a PINO radical from the NHPI.^{6a} Accordingly, the $\text{Co}(\text{III})$ which



fails to react with O_2 could not promote the reaction under O_2 at rt (Run 2).^{6a,7}

From 1,3-dioxolane (1b), the corresponding adduct 3b was obtained in high yield (82%) (Run 4). The introduction of the masked formyl group to 2a is promising, since the direct use of formaldehyde is restricted due to its intractability. These dioxolane moieties could be easily deprotected upon treatment under acidic conditions to form the corresponding carbonyl compounds [eqns. (3) and (4)].



The reaction of 1a or 1b with various alkenes was run under selected reaction conditions (Table 2). Acrylonitrile (2e) was found to serve as a good acceptor of 1a and 1b in a similar manner as 2a, giving cyanohydrin derivatives in good yields. However, methyl crotonate (2c) bearing a β -methyl group retarded the hydroxyacylation, probably owing to the steric hindrance towards attack by an α,α -dioxalkyl radical on 2c.⁸ To our surprise, methyl vinyl ketone (5a) reacted with 1a to afford a cleaved product, 3-(1,3-dioxolan-2-yl)butanoic acid (6) in 83% yield along with 3-(1,3-dioxolan-2-yl)butylaldehyde (7)

Table 1 Reaction of 1a–c with methyl acrylate (2a)^a

Run	1a–c	NHPI/ mol%	Co(II)/ mol%	t/h	Yield (%) ^b
1	1a	5	0.05	3	81
2 ^c	1a	5	0.05	3	n.d.
3	1a	—	0.05	3	1
4 ^d	1b	10	0.1	2	82
5	1c	5	0.1	14	76

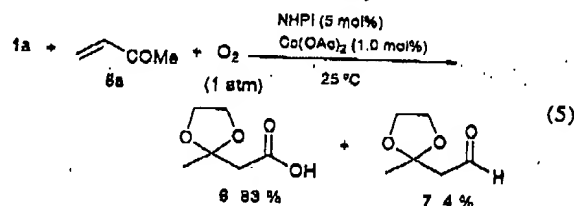
^a 2a (3 mmol) was allowed to react with 1a–c (15 mmol) in the presence of NHPI and $\text{Co}(\text{OAc})_2$ under atmospheric oxygen at rt. ^b GC yield. ^c $\text{Co}(\text{acac})_3$ was used. ^d 1b (30 mmol) was used.

Table 3. Reaction of 1a-b with various alkenes under ambient conditions^a

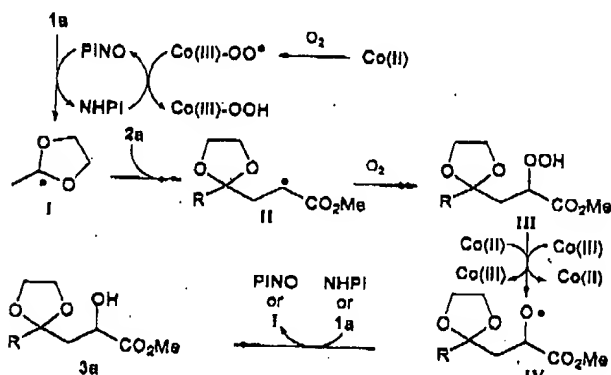
$1a-b + R^2-CH=CH-R^3 + O_2 \xrightarrow[25^\circ C]{NHPi (5 \text{ mol}\%), Co(OAc)_2 (0.1 \text{ mol}\%)} \text{Product}$							
Run	1a-b	R ²	R ³	R ⁴	2b-e	t/h	3 (%) ^b
1	1a	H	Me	CO ₂ Me	2b	15	84
2 ^c	1a	Me	H	CO ₂ Me	2c	15	16
3 ^d	1a	CO ₂ Et	H	CO ₂ Et	2d	2	77
4	1a	H	H	CN	2e	16	77 ^e
5	1b	H	Me	CO ₂ Me	2d	15	60
6	1b	H	H	CN	2e	16	60 ^e

^a 2b-e (3 mmol) were allowed to react with 1a-b (15 mmol) in the presence of NHPi (5 mol%) and Co(OAc)₂ (0.1 mol%) under atmospheric oxygen at rt. ^b GC yield. ^c NHPi (10 mol%) was used. ^d Co(OAc)₂ (0.05 mol%) was used. ^e Isolated yield.

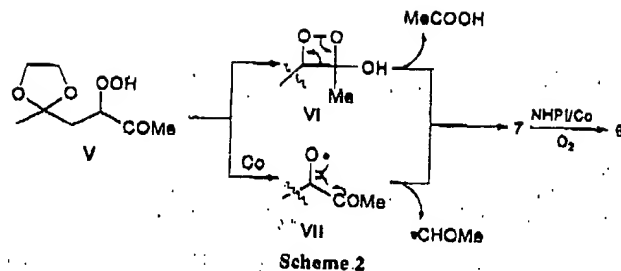
(4%) [eqn. (5)]. The carboxylic acid 6 is considered to be formed via the further oxidation of aldehyde 7.⁹



A plausible reaction path for the apparent hydroxyacylation of 2a with 1a under dioxygen is shown in Scheme 1. The reaction may be initiated by the hydrogen atom abstraction from NHPi by the action of the Co(III)-dioxygen complex, giving PINO which then abstracts the dioxolane hydrogen of the 1a to form an dioxolane radical I. The I radical having a highly nucleophilic character seems to readily add to 2a, yielding a radical species II. Under the conditions in which O₂ is present in the reaction system, the resulting radical II is rapidly trapped by O₂ to give a hydroperoxide III. It is well-known that hydroperoxides like III are subjected to redox decomposition by Co ions to form an alkoxy radical IV which is eventually



Scheme 1 Proposed reaction path for the radical addition of 1a to 2a under dioxygen in the presence of NHPi and Co(OAc)₂.



Scheme 2

converted into 3a through the hydrogen abstraction from either NHPi or 1a.¹⁰

Although it seems rather hazardous to make an accurate assessment about the reaction path for the formation of 6 from 1a and methyl vinyl ketone 5a, we can make two proposals which seem to agree with the experimental results. It is probable that an α -hydroperoxyketone V derived from 1a and 5a might decompose into aldehyde 7 via formation of a hydroxydioxetane VI (Scheme 2). This type of reaction through the hydroxydioxetane is shown in the autooxidation of ketones like diisopropyl ketone.¹¹ However, an alternative proposal is also possible, viz. the hydroperoxide V is subject to the redox decomposition to generate an alkoxy radical intermediate VII which then is converted into 7 via β -scission.

In conclusion, we have developed a novel method for the introduction of both a masked acyl or formyl group and a hydroxy or keto function to a double bond of alkenes. Further work on the extension of this method is actively underway.

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Notes and references

[†] A typical procedure for reaction of 2-methyl-1,3-dioxolane 1a with methyl acrylate 2a: To a solution of 1a (15 mmol), NHPi (0.15 mmol) and Co(OAc)₂ (0.0015 mmol) in a two-necked flask, equipped with a balloon filled with O₂ (1 atm), was added 2a (3 mmol). The mixture was vigorously stirred at rt for 3 h. The recovery of unreacted 1a under a reduced pressure followed by flash chromatography on silica gel (*n*-hexane-AcOEt = 1:2) afforded methyl 2-hydroxy-4-(1,3-dioxolan-2-yl)valerate (3a) (462 mg, 81% yield) as a colorless liquid.

- Recent review: C.-H. Jun, J.-B. Hong and D.-Y. Lee, *Synlett*, 1999, 1.
- M. Tracy and Jr. Patrick, *J. Org. Chem.*, 1952, 17, 1009.
- M. Braun, *Angew. Chem., Int. Ed. Engl.*, 1987, 26, 24; C. H. Heathcock, *Comprehensive Carbocation Chemistry*, ed. E. Buncl and T. Durst, Elsevier, Amsterdam, 1984, Chap. 4.
- T. Punniyamurthy, B. Bhatia and J. Iqbal, *J. Org. Chem.*, 1994, 59, 850.
- The use of dioxolanones as masked aldehydes has been extensively studied: H.-S. Dang and B. P. Roberts, *Tetrahedron Lett.*, 1999, 40, 8929; A. Gross, L. Fensterbank, S. Bogen, R. Thouvenot and M. Malacria, *Tetrahedron*, 1997, 53, 13797.
- (a) Y. Yoshino, Y. Hayashi, T. Iwahama, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 1997, 62, 6810; (b) S. Sakaguchi, T. Takase, T. Iwahama and Y. Ishii, *Chem. Commun.*, 1998, 2037, and references therein.
- E. C. Niederhoffer, J. H. Timmons and A. E. Martell, *Chem. Rev.*, 1984, 84, 137.
- B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1983, 22, 753.
- We have reported that aldehydes are readily oxidized to corresponding carboxylic acids with dioxygen by the NHPi-Co(OAc)₂ system under ambient conditions: T. Iwahama, Y. Yoshino, T. Kaitoku, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2000, in print.
- R. A. Sheldon and J. K. Kochl, *Metal-Catalyzed Oxidation of Organic Compounds*, Academic Press, New York, 1981.
- W. Adam, *The Chemistry of Peroxide*, ed. S. Patai, John Wiley & Sons, New York, 1983, p. 830.